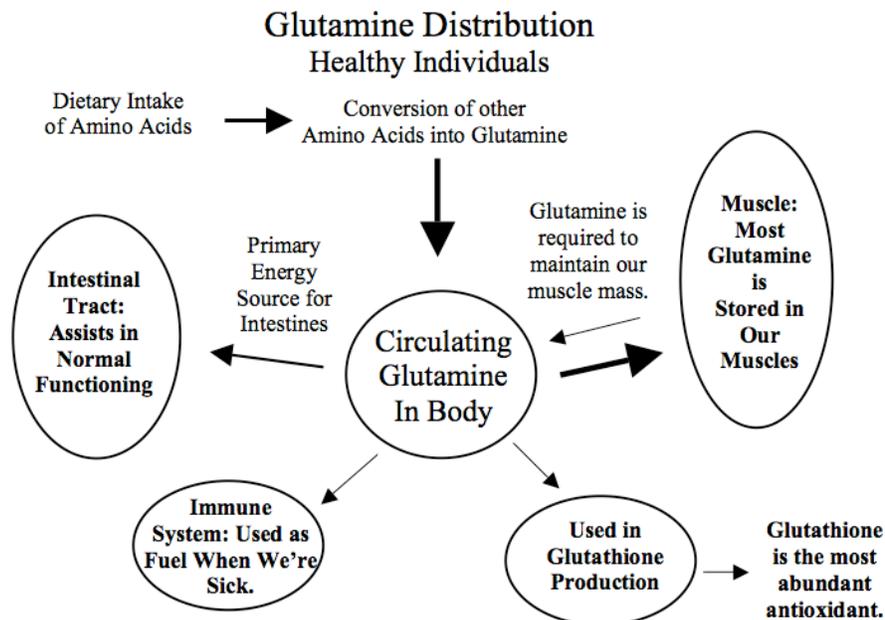


The Importance of Glutamine and Antioxidant Vitamin Supplementation in HIV

An Introduction to Glutamine

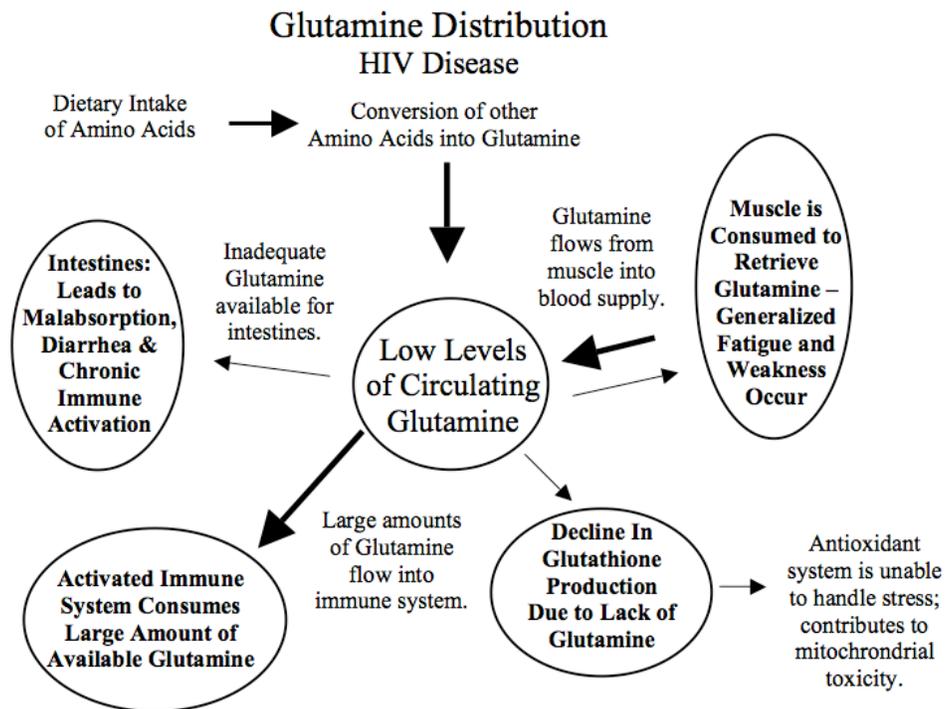
Glutamine is the most abundant amino acid in the human body, and plays extremely important role in the functioning of most cells within the body. There is growing evidence that glutamine deficiency is responsible for several of the nutritional disorders commonly found in a variety of medical conditions such as severe burns, intensive care unit (ICU) patients, bone marrow transplantation, inflammatory bowel disorders and chronic HIV infection.

Eighty percent of the available amino acids in the body are in the form of glutamine. Glutamine is either stored in the muscle or is freely available circulating within the blood stream where it is available for uptake by a variety of cells in the body. Many different cell types in your body are dependent upon glutamine either as a form of energy or to maintain a healthy level of antioxidants within the cellular material of the cells. The major intracellular antioxidant is known as glutathione and requires glutamine for its production. Below is a schematic outlining the distribution of glutamine in your body.



An average diet contains very little glutamine. Glutamine is found in most animal muscle but is quickly destroyed when we cook our food. Therefore, the body obtains most of its glutamine by converting other absorbed dietary amino acids into glutamine. This ability to convert other amino acids into glutamine allows the body to produce sufficient quantities of glutamine and is why glutamine is known as a non-essential amino acid.

Individuals who have medical conditions with high rates of immune activation (HIV Disease, Crohn's Disease, Ulcerative Colitis, severe burn recovery, and cancer chemotherapy recipients) are often unable to produce enough glutamine to meet the immune system's increased glutamine requirements and this leads to a state of chronic glutamine deficiency. The schematic below depicts how the excessively high rate of immune activation causes a shift in the bodies glutamine distribution and consequently leads to depletion of muscle mass, malabsorption, diarrhea and failure of the antioxidant system.



The chronic deficiency of glutamine results in the body's inability to perform critical functions such as:

1. Maintain adequate stores of skeletal muscle.
2. Provide energy for many components of the immune system such as CD4 lymphocytes and macrophages.
3. Maintain stores of vital intracellular antioxidants such as glutathione.
4. Maintenance of proper absorption function and integrity of the intestinal tract.
5. Eliminate waste from catabolism of protein throughout the body.

Chronic Immune Activation, Intestinal Health and HIV infection

Chronic immune activation is slowly becoming understood as a major source of the cellular stress and damage associated with HIV infection. Recent research has demonstrated that the degree of immune activation a patient sustains from chronic HIV infection is the most important factor in determining the progressive decline in immune function associated with the development of AIDS. The degree of immune activation as measured by CD38 lymphocytes is a more accurate predictor of declining CD4 counts than even HIV viral load (HIV RNA) levels.

The immune system is designed to be activated in a very specific and particular manner depending on the type of infection it's dealing with. Small amounts of specific immune system signaling hormones and chemicals are used to enhance or activate particular components and then are turned off after the infection is cleared from the body.

The immune activation associated with HIV infection is a massive and uncoordinated release of immune signaling chemicals that results in the immune system from reacting efficiently on a broad scale. The immune system is unable to react to simple vaccines appropriately, control the production of antibodies against common bacteria, assist in the prevention of cancers through tumor surveillance, recall prior immunity from previous infectious episodes and trigger inflammation and swelling associated with many infections.

Excessive immune activation also results in the immune system in over-responding and results in potentially deadly inflammatory reactions in the kidney and liver as well as increase rates of heart attacks that are commonly triggered by inflammation.

Unfortunately for many patients, their immune system's activation level doesn't normalize after complete suppression of HIV. This has led to speculation that the immune system may be permanently damaged. Recent studies have demonstrated that the persistent immune activation after HIV suppression is originating from the immunological tissue surrounding the small intestine known as the gastrointestinal-associated lymphoid tissue (GALT).

The cells that line the small intestine normally are connected to each other with very tight seams that prevent any unwanted materials such as bacteria or their by-products from leaking into the GALT environment. Unfortunately, patients chronically infected with HIV develop leakage between the cells of the intestinal tract and allow bacterial by-products into the GALT region.

These bacterial by-products, known as lipopolysaccharides (LPS) are highly immunogenic and lead to chronic stimulation of the immune system. It is not understood why bacterial translocation occurs but it is seen in other patients with chronically activated immune systems and glutamine has been shown to improve its negative consequences.

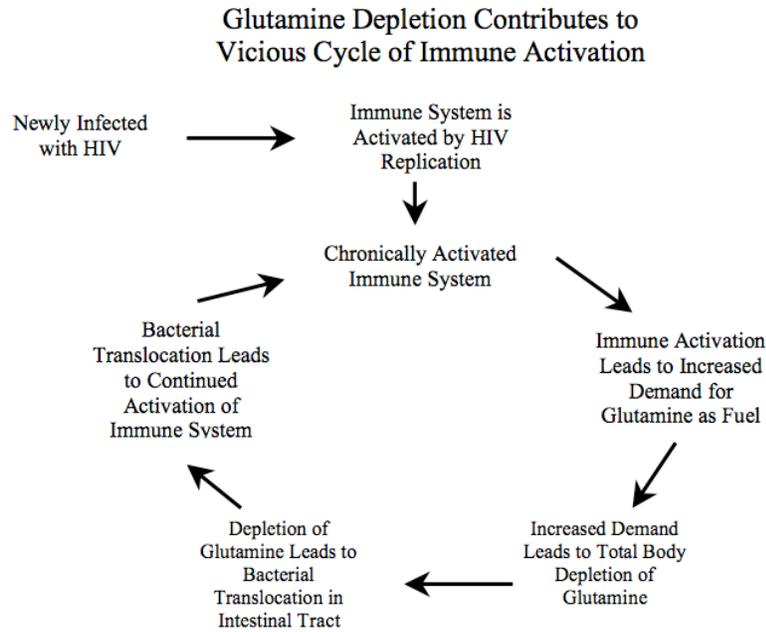
How Glutamine Deficiency May Perpetuate Immune Activation

Several studies have shown that supplementation of glutamine in patients with bacterial translocation results in clinical improvement. Bacterial translocation is known to occur in patients sick enough to be in surgical intensive care unit, receiving chemotherapy and undergoing treatment for severe burns.

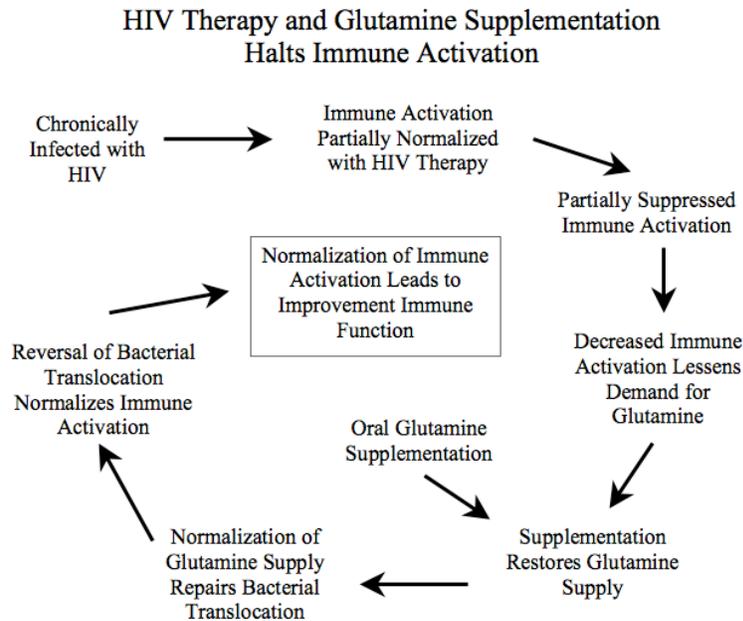
The glutamine deficiency caused by the initial immune activation of chronic HIV replication (outlined above) may have a role in the perpetuation of immune activation after HIV has been completely suppressed. Normally, immune system activation will return to its normal resting state after a viral infection is suppressed or cleared.

In the case of HIV infection, the degree of immune activation seems to be of such intensity that it results in a serious degree of glutamine deficiency that prevents the intestinal tract from remaining healthy enough to avoid the development of bacterial translocation and its associated

immune activation. This creates a self-perpetuating cycle of immune activation leading to glutamine deficiency, leading to bacterial translocation, leading to immune activation, leading to further glutamine deficiency (see below).



Daily supplementation of glutamine of approximately 0.4 gram of glutamine/kilogram of body weight (approximately 30 grams of glutamine for a 170 lb p[erson]) has been shown to improve bacterial translocation in other medical conditions associated with chronic immune activation and bacterial translocation.



HIV-related Malabsorption, Diarrhea and Glutamine Supplementation

In HIV Disease, glutamine deficiency has been clearly documented in the scientific literature, and very likely contributes to intestinal malabsorption, wasting of skeletal muscle, low antioxidant levels (glutathione) as well as poor CD4 lymphocyte function.

Malabsorption has been found to occur in approximately 50% of patients without any intestinal tract symptoms and upwards of 90% of all patients infected with HIV. Studies show that patients with other high metabolism diseases such as chemotherapy, radiation therapy, Crohn's Disease, Ulcerative Colitis, a variety pediatric intestinal diseases and recovery from severe burns also have high frequency of malabsorption.

The common metabolic abnormality among these medical conditions is a state of glutamine deficiency caused by increased demand for glutamine through immune activation combined with the body's limited ability to produce glutamine to meet this increased demand. The resultant glutamine deficiency results in a lack of energy and protein substrate for cells that make up the absorptive lining of the small intestine resulting in the body's inability to adequately absorb nutrients such as sugars, fats, protein, vitamins and minerals.

Malabsorptive diarrhea is the result of incomplete absorption of nutrients that are passed into the distant part of the small intestine. A variety of bacteria that live in the distant small intestine and colon ingest these nutrients and produce gas and other products that cause the stool to be watery and loose.

Scientific studies have also demonstrated that supplementation with glutamine improves the health and absorptive ability of intestinal tract resulting in fewer hospitalizations, decreased length of hospitalizations, fewer bacterial infections and improved gastrointestinal functioning with a decrease or resolution of diarrhea and improved nutrition.

Glutamine supplementation has also demonstrated improvement of intestinal absorption by stimulating the re-establishment of the cells lining the intestine. The rejuvenation of the intestine results in significant improvements in stool formation and the reduction of diarrhea.

Wasting Syndrome and Glutamine Utilization

Wasting Syndrome in HIV is a multitude of disorders associated with the loss of weight in individuals infected with HIV infection. Since the creation of the term Wasting Syndrome, many of the separate disorders have contributed to the weight loss associated with Wasting Syndrome have been discovered, and are readily being treated in most HIV specialty practices. Some of these disorders are testosterone deficiency, poor appetite (depression, smoking, medications, hormone deficiencies), as well as a variety of chronic infections (sinus, intestine, oral and esophageal candidiasis).

Even with the treatment of these conditions, a substantial number of patients continue to burn abnormally high amounts of body cell mass (muscle and organ protein) for energy when losing weight instead of burning fat. In addition, these same individuals have a tendency of regaining a predominance of fat.

Recent studies from Washington University School of Medicine in St. Louis, Missouri discovered that individuals with HIV infection have a high rate of glutamine depletion from their muscles, and a very low rate of glutamine replenishment after eating compared to HIV negative individuals. The study also showed that in spite of the rapid loss of stored glutamine from the muscle, the body's other organs consume glutamine so quickly that glutamine blood levels remained abnormally low.

Since muscle is the primary storage site of glutamine in the body, the increased rate of breakdown of muscle-stored glutamine is what one would expect when the available pool of circulating glutamine is rapidly being depleted by the high metabolic rate of cells involved with HIV infection. The inadequate supply of dietary glutamine also contributes to the abnormally low level of available circulating glutamine.

Body Cell Mass Improvement with Glutamine Supplementation

As discussed above, the body's physiological drive to maintain an adequate supply of glutamine for organ and cellular function may be responsible for the excessive depletion of muscle mass in HIV Disease, and the accompanying difficulty of restoring muscle mass when weight is regained. Several studies now support the use of a glutamine-containing supplement in effort to improve body cell mass of patients with HIV Disease.

A placebo-controlled clinical trial provided 40 grams of glutamine and antioxidant supplement daily to patients with Wasting Syndrome who had lost 10% or more of their weight. After a three-month period, the glutamine treatment group gained 4.8 lbs. total weight and 4.0 lbs. of body cell mass. The placebo group gained 0.66 lbs. and 0.88 lbs. of total weight and body cell mass respectively.

The body cell mass gains in these patients was at a rate only previously seen in studies of Wasting Syndrome patients treated with anabolic steroids or human recombinant growth hormone. Prior studies of glutamine supplementation in otherwise healthy, HIV-negative individuals showed no significant gains in muscle or body cell mass.

Researchers believe the glutamine supplementation improves body cell mass because the body finally has an adequate supply of glutamine to replenish its depleted glutamine muscle stores.

Glutamine Supplementation and CD4 Lymphocyte Function

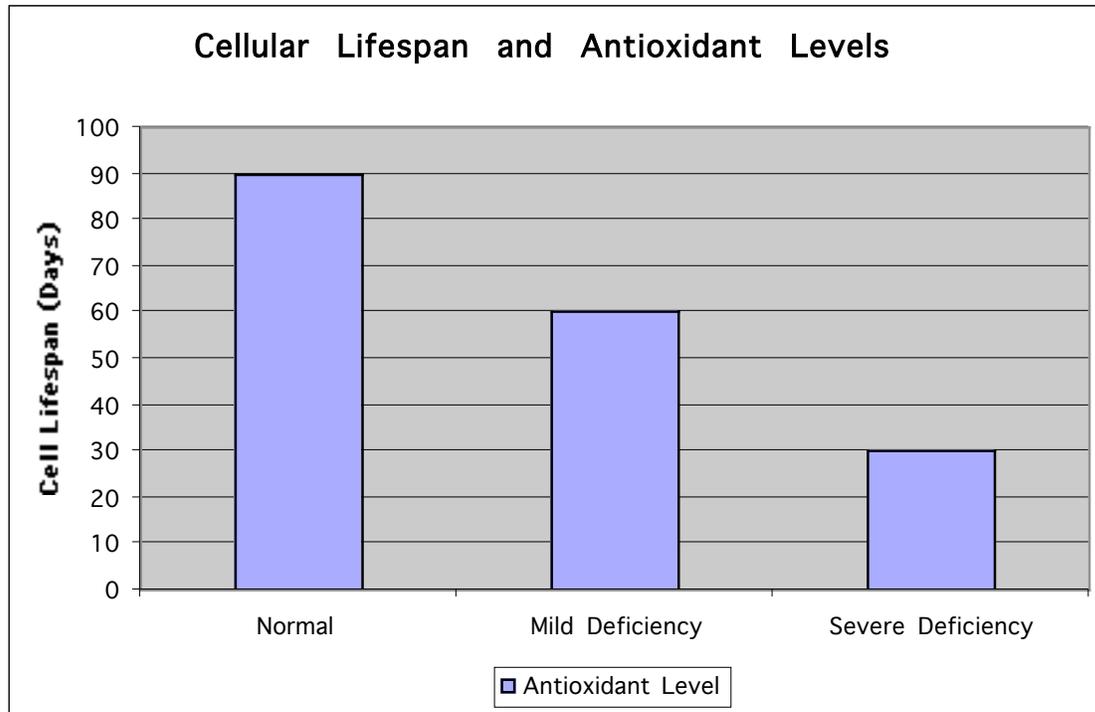
CD4 lymphocytes are under a great level of stress during HIV infection because they are predominantly being infected and destroyed by HIV. They are also responsible for directing a large part of immunological response against HIV. In an untreated HIV-infected patient, the body is required to produce 500 million to 2 billion CD4 lymphocytes daily to replace those cells that are being destroyed by HIV.

Studies in the laboratory have demonstrated that CD4 lymphocytes from HIV-infected individuals are often depleted of glutamine and glutathione, the antioxidant produced from glutamine. When these cells are supplemented with adequate levels of glutamine, significant improvements in the CD4 lymphocyte function occur. One clinical trial demonstrated that consistent use of glutamine for 1 year resulted in a 15% increase in CD4 lymphocyte counts.

Glutamine Improves the Glutathione Levels

Finally, several studies on patients with HIV Disease have documented the depletion of intracellular levels of glutathione, the most abundant antioxidant available in all of our cells. Decreased levels of glutathione are associated with decreased survival in HIV, and replacement therapies for glutathione have been associated with trends towards improvement in survival in HIV.

One of the key building blocks for the production of glutathione is glutamine, and without adequate supplies of glutamine, the body is unable to produce adequate amounts of glutathione. Glutamine and N-acetyl cysteine supplementation have been both shown to significantly improve intracellular levels of glutathione within patients with HIV infection.



The Importance of Adequate Antioxidant Supplies in HIV Disease

Antioxidants are important in that they help to repair the normal damage that occurs in cells of our bodies. Glutathione is the most abundant antioxidant in the body, and is involved with the maintenance and repair of various components of the cells membrane and structural components.

Other well-known antioxidants are vitamins and minerals and are involved in maintaining and repairing the broad array of enzymes within our body's cells. Some of these enzymatic antioxidants are Vitamin C, Vitamin A and it's precursor Beta-carotene, selenium and Vitamin E.

Studies in HIV Disease have demonstrated a decreased survival when any of these vitamin or mineral antioxidants is deficient. Likewise, many studies have shown increase in survival when any of these particular antioxidants are replaced in patients who are deficient.

What happens if the cellular levels of antioxidants are low?

Science has demonstrated that deficient antioxidant levels result in inefficient cellular function and more rapid cell death. Inefficient enzyme function can lead to deficient production of important cellular chemicals or potentially to accidental misreading of genetic material leading to the formation of a cancerous or nonfunctioning cell. Inadequate formation of glutathione is believed to contribute poor cell function and a decreased cell life span as illustrated in the following example.

For the sake of illustrating a point, assume the body produces an important cell every day, and that to be healthy, the body requires each new cell to live a total of 90 days. Now, lets also assume that these cells die after they are 90 days old. So on an ongoing basis, the body would have one cell being made every day and one dying every day for a total of 90 cells circulating (as depicted in the following diagram).

Now lets assume the body has a mild deficiency of antioxidants, these same cells are less healthy and are only able to live 60 days. So now the body has only 60 cells available instead of 90 at any given time. The figure above also shows the possible scenario with severe deficiency of antioxidants that might result in only 30 cells circulating when the body produces, and requires 90 cells of this type to function properly.

This is one of the common ways that antioxidants are important in maintaining cellular function and clearly there is some concern that low levels of antioxidants may be effecting the immunological function of the vast array of cells needs to combat HIV and its complications.

Concluding Remarks about Glutamine and Antioxidants

In conclusion, the data is accumulating rapidly to support ongoing supplementation of glutamine at approximately 0.25 grams of glutamine per pound of body weight per day. This means that the average size man weighing will need about 30-40 grams or 6-8 teaspoons (2 to 2 2/3 tablespoons) of powdered glutamine in his diet per day.

Additionally, high levels of antioxidant supplementation are required by patients. This should not be obtained by simply taking several multi-vitamins on a daily basis because potential for excess iron toxicity on the liver. A good multi-vitamin with high levels of antioxidants (Vitamin C and beta Carotene) and preferably with high levels of B-complex vitamins is ideal for HIV Disease in addition with approximately 30 gram a day dose of glutamine.

If a patient with HIV infection is having active diarrhea, they should take approximately 40 - 60 grams of glutamine until the diarrhea improves; this can take approximately 1 – 6 weeks. The dose is then decrease to a daily maintenance dose of 2 tablespoons of glutamine daily.